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EXAMINER	
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ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/540,612	FARNEGARDH ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,29-32,35 and 40-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,29-32,35 and 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/18/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

In response to the previous Office action, a non-Final rejection (mailed on 11/30/2007), Applicants filed a response and amendment received on 05/30/2008. Said amendment canceled Claims 13-28, 33, 34 and 36-39, and amended Claims 1-10, 29 and 30, and added claims 40-45. Thus, Claims 1-12, 29-32, 35 and 40-45 are at issue and present for examination.

Applicants' arguments filed on 05/30/2008, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Objections to the Specification

The previous objection of the specification for not mentioning SEQ ID NOs is withdrawn by virtue of Applicants' amendment, wherein Applicants have inserted all SEQ ID NOs: 1-24.

Claim Objections

The previous objection of Claims 1-4, 6-10, 29 and 30 for not writing out the abbreviation "LXRβ" is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 7 for the recitations of "T0901317" and "GW3965" is withdrawn by virtue of Applicants amendment wherein Applicants have replace the noted terms with "N-(2,2,2-trifluoroethyl)-N-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide," and "3-(3-(2-chloro-3-trifluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid," respectively.

The previous objection of Claims 9-10 for not writing out the abbreviation "LBD" is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 9 for missing commas after unit cell dimension a and b is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 10 for missing "angstrom" after each unit cell dimensions a, b, and c is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 10 for not having proper subscripts in the space group "P21212" is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 10 for the recitation of "LXRI3" is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 29 for missing a conjunction between "Leu453," and "Trp457" is withdrawn by virtue of Applicants' amendment.

The previous objection of Claim 31 for containing a non-elected invention, i.e., Figure 5b and SEQ ID NO: 2, is withdrawn because SEQ ID NO: 2 is a species of SEQ ID NO: 1.

Claims 1, 2, 6, 10, 29-31, 40-42 and 44 are objected to because of the following informalities:

Claims 1, 2, 40 and 41 are objected to for the recitation of "shown in Figure 5a (SEQ ID NO: 1)", which can be improved with respect to form. The Examiner suggests replacing the noted phrase with ---as set forth in SEQ ID NO: 1---.

Claims 1, 6, 29, 40 and 44 are objected to for containing a misspelling in "3-(3-(2-chloro-3-trufluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid" (underlined for added emphasis). The Examiner suggests replacing it with "3-(3-(2-chloro-3-trifluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid."

Claims 4, 5 and 7 are objected to for the recitation of "wherein said crystal belongs to space group ...," which can be improved with respect to form and clarity. The Examiner suggests replacing the noted phrase with ---wherein said crystal belonging to the space group ...---.

Claims 10 and 40 are objected to for the recitation of "NR box of TIF2" which can be improved with respect to form and clarity. The abbreviations "NR" and "TIF2" need to be written out in full. In addition, since the recitation inside the parenthesis is not clear as to whether or not it should be treated as a claim limitation, the Examiner suggests deleting the parenthesis. In the interest of advancing prosecution, the

recitation inside the parenthesis is considered as a mere example and not as a claim limitation.

Claims 29 and 30 are objected to for containing typographical errors, i.e., "Thr2n" and "Va1439". The Examiner suggests correcting these to ---Thr272--- and ---Val439--- according to pg. 10 of the specification.

Claims 29 and 30 are objected to for containing typographical errors, i.e., "form". The Examiner suggests replacing "form" with ---from---.

Claim 31 is objected to for the recitation of "in Figure 5a (SEQ ID NO: 1)" and "in Figure 5b (SEQ ID NO: 2)", which can be improved with respect to form. The Examiner suggests replacing the noted phrase with ---as set forth in SEQ ID NO: 1 [or 2]---.

Claim 42 is objected to for missing "angstrom" symbols after each unit cell dimensions a, b, and c.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 29-32, 35, 40-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 8-10, 29, 30, 40-42, 44 and 45 (4-7, 11, 12, 35 and 43 dependent therefrom) recite the phrase, "LXRβ ligand binding domain" or "LBD," which are unclear and indefinite.

Although Applicants allege that it refers explicitly to an LXR beta ligand binding domain that contains the amino acid sequence from Leu220 to Glu461 of SEQ ID NO: 1, it is noted by the Examiner that as amended, it also refers to "an amino acid sequence having at least 95% sequence homology to the Leu220 to Glu461 of human LXRβ" (see claim 1 and 40) or "a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more than 1.5 Å" (see claims 29, 30, 44 and 45). As such, it is unclear which residues of [1] an amino acid sequence having at least 95% sequence homology to the Leu220 to Glu461 of human LXRβ, or [2] a homologue, constitute such a domain. Furthermore, contrary to Applicants' allegation, it is noted by the Examiner that the LXRβ LBD of claims 8-10 remain to be undefined. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

The previous rejection of Claim 7 under 112 2nd paragraph for reciting the phrase, "the internal "LXRβ binding cavity," is withdrawn by virtue of Applicants' amendment which deleted the phrase.

The previous rejection of Claim 2 under 112 2nd paragraph for reciting the phrase, "an amino acid sequence having at least 95% identity with the sequence and

which encodes for LXRβ ligand binding domain," is withdrawn by virtue of Applicants' amendment which deleted the phrase.

The previous rejection of Claim 29 under 112 2nd paragraph for reciting the phrase, "the coordinate tables," is withdrawn by virtue of Applicants' amendment which deleted the phrase.

Claims 1 and 40 (2-7, 11, 12 and 41 dependent therefrom) recite the phrase, "a polypeptide comprising [or having] an amino acid sequence at least 95% identical to the sequence from Leu220 to Glu461 of human LXRβ (SEQ ID NO: 1)" which is unclear and indefinite. It is unclear with respect to which sequence "Leu220 to Glu461" is referring to because there is no reference sequence recited in the claim. The Examiner suggests deleting the parenthesis around "SEQ ID NO: 1" and amend the claim so that the claim clearly indicates a reference sequence, i.e., Leu220 to Glu461 of human LXRβ as set forth in SEQ ID NO: 1, to overcome this rejection.

Claim 7 recites the phrase, "wherein said crystal belongs to space group $P6_122$ and has the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3Å or a=58.7Å, b=98.9Å, c=175.8Å wherein α=β=90°, γ=120°" which is unclear and indefinite. It is not clear how a crystal, having the same polypeptide sequence, the same space group, and the same bond angles, can have a vastly different unit cell dimensions, i.e., a=58.7Å, b=98.9Å, c=175.8Å.

Claim 32 recites the phrase, "such as his tag" which is unclear and indefinite. The phrase "such as" renders the claim indefinite because it is unclear whether the

limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 40 recites the phrase, "said LXRβ ligand being chosen from ... or N-[1-(2-furanyl)ethyl]-N-4-pyridinyl-tricyclo [3.3.1.13,7] decane-1-carboxamide Liver X receptor beta ligand binding domain (LXRβ LBD)" which is unclear and indefinite. It is unclear what kind of ligand "N-[1-(2- furanyl)ethyl]-N-4-pyridinyl-tricyclo [3.3.1.13,7] decane-1-carboxamide Liver X receptor beta ligand binding domain (LXRβ LBD)" is. In the interest of advancing prosecution, the ligand is interpreted as "N-[1-(2- furanyl)ethyl]-N-4-pyridinyl-tricyclo [3.3.1.13,7] decane-1-carboxamide".

Claim 43 recites the phrase, "The crystallized molecule or molecular complex of claim 29 or 30, wherein said binding pocket was resolved by molecular replacements using the structure of a thyroid hormone receptor as a search model" which is unclear and indefinite. Although structures coordinates of a 3-D structure *in silico* can be resolved by molecular replacement using a 3-D structure of a different protein, i.e., thyroid hormone receptor, It is unclear how a crystal/crystal complex can be resolved by an *in silico* method. In the interest of advancing prosecution, the phrase, "wherein said binding pocket was resolved by molecular replacements using the structure of a thyroid hormone receptor as a search model" is not given a patentable weight.

It is suggested that Applicants clarify the meaning of noted phrases.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 29, 30 and 40-45 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-12, 29, 30 and 40-45 are rejected because the amendment to claims, filed on 05/30/2008, contains new matter.

Claim 1 recites, "a crystal belonging to space group $P6_122$, wherein said LXRβ LBD comprises...a polypeptide comprising an amino acid sequence at least 95% identical to the sequence from Leu220 to Glu461," which is new matter. The reason is that Applicants only provide support for 4 crystals (2 crystals with space group $P2_12_12_1$, 1 crystal with space group $P6_122$, and 1 crystal with space group $P2_12_12$) having the specific amino acid sequence, space group, unit cell dimensions and bond angles as disclosed in pages 6 and 24, and Table 1. In light of the notion that obtaining X-ray diffraction quality crystals is highly unpredictable (see previous enablement rejection with regard to the general knowledge of prior art: unpredictability associated with making X-ray diffraction quality crystals), a genus of crystals comprising an amino acid sequence at least 95% identical to the sequence from Leu220 to Glu461, i.e., those sequences having any ~12 amino acid residues mutated/modified at any location, is not

supported by the instant specification at the time of filing and one of skill in the art would not have recognized that Applicants were in possession of the recited invention as claimed. It is noted by the Examiner that the phrase, "wherein said polypeptide is capable of binding to ... [3 compound names]" is interpreted as characteristics of said polypeptide, which means that the genus of crystals as claimed is not a co-crystal complex with these compounds.

Regarding claim 6, the recitation of "The crystal according to claim 1 or 3, further comprising 3-(3-(2-chloro-3-trufluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid bound to the LXRβ LBD" is new matter. First, the specification does not provide support for a co-crystal comprising LXRβ LBD and 3-(3-(2-chloro-3-trufluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid, which has a space group $P6_122$. Furthermore, as claim 6 depends from claim 3 in the alternative, the specification lacks support for a co-crystal comprising LXRβ LBD and 2 ligands, N-(2,2,2-trifluoroethyl)-N-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide and 3-(3-(2-chloro-3-trufluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid.

Regarding claim 7, the recitation of "wherein said crystal belongs to space group $P6_122$ and has the unit cell dimensions ...or *a= 58.7 A, b = 98.9 A, c = 175.8 A*," which is new matter. The specification lacks support for a crystal of LXRβ LBD having space group $P6_122$ with the unit cell dimensions, a= 58.7 A, b = 98.9 A, c = 175.8 A.

Claims 1-12, 29, 30 and 40-45 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 1-12, 29, 30, 32 and 35. In response to this rejection, Applicants have amended Claims 1-10, 29 and 30, and added claims 40-45, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that unlike the Office' s characterization that only two representative structures of the claimed crystals were disclosed, the specification actually discloses two sets of crystals for the complex of LXRβ LBD and T0901317 having space groups $P2_12_12_1$ and $P6_122$ (see specification at paragraph [0125] of US 0710060740); one crystal structure of the complex of LXRβ LBD and GW9365 having space group $P6_122$ (see specification at Table 1); and one crystal structure of the complex of LXR beta LBD and NR box 1 of TIF2 having space group $P2_12_12_1$ (see specification at paragraph [0020] of US 0710060740). Therefore, four representative crystal structures LXR beta LBD in three different complexes with space groups either $P2_12_12_1$ or $P6_122$ were disclosed in the instant specification, as opposed to "only two representative species," as alleged by the Office. Furthermore, the genus of LXR beta LBD encompassed by the claims does not have substantial variation, since all of the

amino acid sequences must encode a polypeptide having an amino acid sequence identical or highly similar to a reference sequence. Lastly, the claims have been amended to specify the particular ligands and cofactors complexed with the LXR fl LBD, as presently claimed by claims 3, 6, 10 and 40, thus rendering moot the Office's comments. Applicants allege that claims 4-5, 7-10 and 42, as amended herein, are almost identical in scope to hypothetical claim 1 exemplified in case 4 of the "Trilateral Project WM4 Comparative Study on Protein 3-Dimensional (3-D) Structure Related Claims" released in November 2002 ("Trilateral Report").

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, the scope of claims are analyzed to assess how the genera of inventions as claimed fail to meet the written description requirement under the 35 USC 112 1st paragraph.

The scope of claim 1 encompasses a genus of (A) crystals belonging to space group $P2_12_12_1$, wherein said LXR beta LBD consists essentially of the amino acid sequence from Leu220 to Glu461 or Gly213 to Glu461 of a human LXR beta shown in Figure 5a (SEQ ID NO: 1), *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, wherein said LXR beta LBD is in complex with any ligand, having any unit cell dimensions and any bond angles*; or (B) crystals belonging to space group $P6_122$, wherein said LXR beta LBD comprises the amino acid sequence from Leu220 to Glu461 of a human LXR beta shown in Figure 5a (SEQ ID NO: 1), *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, wherein said*

LXR beta LBD is in complex with any ligand, having any unit cell dimensions and any bond angles, or a polypeptide comprising an amino acid sequence at least 95% identical to the sequence from Leu220 to Glu461 of human LXR beta, optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, wherein said LXR beta LBD is in complex with any ligand, having any unit cell dimensions and bond angles (italicized for added emphasis).

The scope of claim 8 encompasses a genus of crystals of the LXR beta LBD belonging to the space group $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 A, b = 100 +/- 5 A, c = 176 +/- 3 A, alpha = beta = gamma = 90° *wherein said crystals comprise any LXR beta LBD amino acids, optionally in complex with any ligand.*

The scope of claim 9 encompasses a genus of crystals of LXR beta LBD belonging to the space group P6~22 and having the unit cell dimensions a = 59 +/- 3 A, b= 59 +/- 3 A, c = 294 +/- 3 A, alpha = beta = 90°, gamma = 120°, *wherein said crystals comprise any LXR beta LBD amino acids, optionally in complex with any ligand.*

The scope of claim 10 encompasses a genus of crystals of LXR beta LBD in complex with *any coactivator peptide* belonging to the space group $P2_12_12_1$ and having the unit cell dimensions a = 89 +/- 3 A, b = 91 +/- 3 A, c = 131 +/- 3 A, alpha = beta = gamma = 90°, *wherein said crystals comprise any LXR beta LBD amino acids, optionally in complex with any ligand.*

The scope of claim 29 encompasses a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structural coordinates of human LXR beta LBD comprising amino acid residues Ser242, Phe268, Phe271,

Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Val439, Leu442, Leu449, Leu453, and Trp457, according to the structural coordinates of the complex of LXR beta LBD and 3-(3-(2-chloro-3-trufluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid as shown in Table 2, *wherein said crystallized molecules or molecular complexes comprise any additional amino acids except at those positions that define the LXR beta LBD and characterized by any space group, any unit cell dimensions and any bond angles, or a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 A, wherein said homologue comprise any amino acid side chains for those backbone atoms defined in the binding pocket, and any additional amino acids except at those positions which define the LXR beta LBD, and characterized by any space group, any unit cell dimensions and any bond angles, wherein said binding pocket is in complex with any ligand.*

The scope of claim 30 encompasses a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structural coordinates of human LXR beta LBD comprising amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Val439, Leu442, Leu449, Leu453, and Trp457, according to the complex LXR beta LBD and N-(2,2,2-trifluoroethyl)-N-[4[2,2,2- trifluoro-l-hydroxy-1-

(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide as shown in Table 2, *wherein said crystallized molecules or molecular complexes comprise any additional amino acids except at those positions that define the LXR beta LBD and characterized by any space group, any unit cell dimensions and any bond angles, or a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 A, wherein said homologue comprise any amino acid side chains for those backbone atoms defined in the binding pocket, and any additional amino acids except at those positions which define the LXR beta LBD, and characterized by any space group, any unit cell dimensions and any bond angles, wherein said binding pocket is in complex with any ligand.*

The scope of claim 40 encompasses crystals of the LXR beta LBD in complex with *any coactivator peptide,* wherein: said crystal belongs to space group $P2_12_12_1$; and said LXR beta LBD comprises the amino acid sequence from Leu220 to Glu461 of a human LXR beta shown in Figure 5a (SEQ ID NO: 1), *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, wherein said LXR beta LBD is in complex with any ligand, having any unit cell dimensions and any bond angles*, or a polypeptide having an amino acid sequence at least 95% identical to the sequence from Leu220 to Glu461 of a human LXR beta (SEQ ID NO: 1), *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence having at least 95% sequence identity to*

human LXR beta, wherein said LXR beta LBD is in complex with any ligand, having any unit cell dimensions and bond angles.

In light of the notion that obtaining X-ray diffraction quality crystals is highly unpredictable (see previous enablement rejection with regard to the unpredictability associated with making X-ray diffraction quality crystals), the genera of crystals as explained above for each claim is not adequately described in the instant application as previously explained. In addition, as explained in the previous enablement rejection, the general knowledge in the art teaches that an amino acid sequence cannot be theoretically translated into a biologically relevant 3-D structure. For these reasons, one of skill in the art would not have recognized that Applicants were in possession of the genera of crystals as claimed which represent the biologically relevant 3-D structures so that compounds can be screened against such structures to identify a therapeutically useful compounds. It is noted by the Examiner that the specification only describes 4 X-ray diffraction quality crystals (2 crystals with space group $P2_12_12_1$, 1 crystal with space group $P6_122$, and 1 crystal with space group $P2_12_12$) having the specific amino acid sequence, space group, unit cell dimensions and bond angles as disclosed in pages 6 and 24, and Table 1. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Claims 1-12, 29, 30 and 40-45 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a crystal, comprising X-ray diffraction quality crystal of human liver X receptor beta consisting of the contiguous amino acid

residues 220 to 461 of SEQ ID NO: 1 complexed with GW3965, and T0901317, wherein said the crystal has the space group symmetry $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°, or alternatively has the space group $P6_122$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120° that diffracts x-rays to a resolution of less than or equal to 3 angstroms, does not reasonably provide enablement for any crystals as described in the rejection under 112 1st paragraph, written description. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 1-12, 29, 30, 32 and 35. In response to this rejection, Applicants have amended Claims 1-10, 29 and 30, and added claims 40-45, and traverse the rejection as it applies to the newly amended claims.

Applicants point out that the present specification describes how to successfully make crystals of several complexes of LXR beta LBD, such as two sets of crystals for the complex of LXR beta LBD and T0901317 having space groups $P2_12_12_1$ and $P6_122$ (see specification at paragraph [0125] of US 07/0060740); one crystal structure of the complex of LXR beta LBD and GW9365 having space group $P6_122$ (see specification at Table 1); and one crystal structure of the complex of LXR beta LBD and NR box 1 of TIF2 having space group $P2_12_12_1$ (see specification at paragraph [0020] of US 07/0060740). Once the crystallization conditions are established, one of ordinary skilled

in the art could have practiced the claimed invention by routine experimentation by following the teachings provided in the specification. The specification describes methods for expressing and purifying the polypeptides, crystallization and data collection and structure determination and refinement (see e.g., specification at paragraphs [0121-0126] and Table 1). The amino acid sequence and domain characterization of LXR beta LBD are described in the instant application and were known in the art at the time of filing. Detailed structural analysis and predicted location of contact sites was disclosed by Applicants in paragraphs [0089 -0110] of the specification. The three-dimensional coordinates of two representative complexes of LXR beta LBD complexed with T0901317 and GW9365 are also disclosed by the present application. As a result of the present invention, the ligand binding domain of LXR beta was mapped and was shown to include residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, 1le309, Met312, Leul3. Glu315, Thr316, Arg319.1le327, Phe329, Leu330, Tyr335, Phe340. Leu345, Phe349, 1le350, 1le353, Phe354, His435, Gln438, Va1439, Leu442, Leu449, Leu453 and Trp457. Residues important for strong interactions were identified, e.g., His435, and well as residues that can be exploited to develop more potent binding agents (e.g., Phe-271, Thr-272 and Thr-316; see paragraphs [0091- 0097] of the specification). Thus, Applicants allege that they have disclosed (and optimized) several crystallization conditions of the ligand binding domain of LXR beta. The three-dimensional structures of two of these crystals were disclosed, as well as important residues within the binding pocket. Applicants further allege that claims 8-10 (currently also including claims 4-5, 7 and 42, as

amended herein) are directed to crystals of LXR beta LBD having the space parameters and unit cell dimensions specified. Therefore, Applicants argue that these claims are commensurate in scope with hypothetical claim 1 exemplified in case 4 of the Trilateral Report (discussed above).

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. First, the scope of claims are analyzed to assess how the genera of inventions as claimed fail to meet the written description requirement under the 35 USC 112 1st paragraph.

The scope of claim 1 encompasses a genus of (A) crystals belonging to space group $P2_12_12_1$, wherein said LXR beta LBD consists essentially of the amino acid sequence from Leu220 to Glu461 or Gly213 to Glu461 of a human LXR beta shown in Figure 5a (SEQ ID NO: 1), *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, wherein said LXR beta LBD is in complex with any ligand, having any unit cell dimensions and any bond angles*; or (B) crystals belonging to space group $P6_122$, wherein said LXR beta LBD comprises the amino acid sequence from Leu220 to Glu461 of a human LXR beta shown in Figure 5a (SEQ ID NO: 1), *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, wherein said LXR beta LBD is in complex with any ligand, having any unit cell dimensions and any bond angles, or a polypeptide comprising an amino acid sequence at least 95% identical to the sequence from Leu220 to Glu461 of human LXR beta, optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino*

acid sequence, wherein said LXR beta LBD is in complex with any ligand, having any unit cell dimensions and bond angles (italicized for added emphasis).

The scope of claim 8 encompasses a genus of crystals of the LXR beta LBD belonging to the space group $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 A, b = 100 +/- 5 A, c = 176 +/- 3 A, alpha = beta = gamma = 90° *wherein said crystals comprise any LXR beta LBD amino acids, optionally in complex with any ligand.*

The scope of claim 9 encompasses a genus of crystals of LXR beta LBD belonging to the space group P6~22 and having the unit cell dimensions a = 59 +/- 3 A, b= 59 +/- 3 A, c = 294 +/- 3 A, alpha = beta = 90°, gamma = 120°, *wherein said crystals comprise any LXR beta LBD amino acids, optionally in complex with any ligand.*

The scope of claim 10 encompasses a genus of crystals of LXR beta LBD in complex with *any coactivator peptide* belonging to the space group $P2_12_12_1$ and having the unit cell dimensions a = 89 +/- 3 A, b = 91 +/- 3 A, c = 131 +/- 3 A, alpha = beta = gamma = 90°, *wherein said crystals comprise any LXR beta LBD amino acids, optionally in complex with any ligand.*

The scope of claim 29 encompasses a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structural coordinates of human LXR beta LBD comprising amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Val439, Leu442, Leu449, Leu453, and Trp457, according to the structural coordinates of the complex of LXR beta LBD and 3-(3-(2-chloro-3-

trufluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid as shown in Table 2, *wherein said crystallized molecules or molecular complexes comprise any additional amino acids except at those positions that define the LXR beta LBD and characterized by any space group, any unit cell dimensions and any bond angles, or a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 A, wherein said homologue comprise any amino acid side chains for those backbone atoms defined in the binding pocket, and any additional amino acids except at those positions which define the LXR beta LBD, and characterized by any space group, any unit cell dimensions and any bond angles, wherein said binding pocket is in complex with any ligand.*

The scope of claim 30 encompasses a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structural coordinates of human LXR beta LBD comprising amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Val439, Leu442, Leu449, Leu453, and Trp457, according to the complex LXR beta LBD and N-(2,2,2-trifluoroethyl)-N-[4[2,2,2- trifluoro-l-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide as shown in Table 2, *wherein said crystallized molecules or molecular complexes comprise any additional amino acids except at those positions that define the LXR beta LBD and characterized by any space group, any unit cell dimensions and any bond angles, or a homologue of said molecule*

or molecular complex wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 A, wherein said homologue comprise any amino acid side chains for those backbone atoms defined in the binding pocket, and any additional amino acids except at those positions which define the LXR beta LBD, and characterized by any space group, any unit cell dimensions and any bond angles, wherein said binding pocket is in complex with any ligand.

The scope of claim 40 encompasses crystals of the LXR beta LBD in complex with *any coactivator peptide*, wherein: said crystal belongs to space group $P2_12_12_1$; and said LXR beta LBD comprises the amino acid sequence from Leu220 to Glu461 of a human LXR beta shown in Figure 5a (SEQ ID NO: 1), *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence, wherein said LXR beta LBD is in complex with any ligand, having any unit cell dimensions and any bond angles*, or a polypeptide having an amino acid sequence at least 95% identical to the sequence from Leu220 to Glu461 of a human LXR beta (SEQ ID NO: 1), *optionally having any additional amino acid sequences attached to N- and/or C-terminus of said amino acid sequence having at least 95% sequence identity to human LXR beta, wherein said LXR beta LBD is in complex with any ligand, having any unit cell dimensions and bond angles.*

In light of the notion that obtaining X-ray diffraction quality crystals is highly unpredictable (see previous enablement rejection with regard to the unpredictability associated with making X-ray diffraction quality crystals), the scope of crystals as

explained above for each claim is not commensurate with the disclosure provided in the instant application which is limited to 4 X-ray diffraction quality crystals (2 crystals with space group $P2_12_12_1$, 1 crystal with space group $P6_122$, and 1 crystal with space group $P2_12_12$) having the specific amino acid sequence, space group, unit cell dimensions and bond angles as disclosed in pages 6 and 24, and Table 1. In addition, as explained in the previous enablement rejection, the general knowledge in the art teaches that an amino acid sequence cannot be theoretically translated into a biologically relevant 3-D structure. For these reasons, it would require undue experimentation for one of skill in the art make and use the scope of crystals as claimed because one would have to painstakingly determine which of the genera of crystals as described above represent the biologically relevant 3-D structures so that structural studies can be performed in order to identify and synthesize new therapeutic compounds for treatment of atherosclerosis by inducing cholesterol efflux from macrophages/foam cells. It is noted by the Examiner that the specification only describes 4 X-ray diffraction quality crystals (2 crystals with space group $P2_12_12_1$, 1 crystal with space group $P6_122$, and 1 crystal with space group $P2_12_12$) having the specific amino acid sequence, space group, unit cell dimensions and bond angles as disclosed in pages 6 and 24, and Table 1. For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 3, 11, 12, 29-32, 35, 43 and 45 are rejected under 35 U.S.C. § 102(e) as anticipated by Bledsoe et al. (US Patent Application No. 10/418,007, (effective filing date 04/26/2002)).

The rejection was stated in the previous office action as it applied to previous claims 1-6, 11, 12, 29-32 and 35. In response to this rejection, Applicants have amended Claims 1-6, 29 and 30, and added claims 40-45, and traverse the rejection as it applies to the newly amended claims.

Applicants argue that there is no teaching in the Bledsoe priority application of crystal complexes of GW3965 or TIF2 or space groups $P6_122$, thus claims directed to any of these complexes and space groups are novel in view of this reference (e.g., at least claim 1(b), 2, 6, 10, 29 and 40-42). Bledsoe priority application discloses a fragment of human LXR beta from amino acid residues 214-462. Claims 1(a), 31 and 31 are directed to crystal forms or human LXR beta sequences consisting essentially of amino acids 220 to 461 of human LXR beta, which is different from the fragment disclosed in the Bledsoe application. Remaining claims 4-5, 7-10 and 42 are directed to crystal form of LXR beta LBD having the space group and unit cell parameters

specified; none of which is disclosed by the Bledsoe application. Lastly, claims 29 and 30, as amended herein, are directed to crystallized molecular complexes of the LXR beta LBD having the particular structural coordinates of the binding pocket specified. Moreover, new claim 43 further specifies that the binding pocket was solved by molecular replacements using the structure of the hormone receptor as a search model. Neither of these coordinates, nor search model, is disclosed by Bledsoe et al.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. As acknowledged by Applicants, Bledsoe et al. teach the crystal of a ligand binding domain of human LXR beta consisting of contiguous amino acid residues 214-462, bound to T0901317, belonging to space group $P2_12_12_1$, which read on claims 1(a) and 45. Furthermore, "consisting essentially of" is regarded as an "open" language. As such, it allows additional amino acids to be attached to N- and/or C-terminus of Leu220 to Glu461, which reads on the Bledsoe's human LXR beta consisting of amino acid residues 214-462. It is noted by the Examiner that "N-(2,2,2-trifluoroethyl)-N-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide," and "T0901317" are used interchangeably. Claims 29 and 30 are not limited to a specific binding pocket but rather to any homologue having RMS deviation of less than 1.5 A from the backbone atoms. Claim 43 does not further limit claims 29 or 30 (see 112 2nd paragraph above). For the reasons provided herein and in the previous office action, the rejection under this statute is maintained.

Conclusion

Claims 1-12, 29-32, 35 and 40-45 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/

Examiner, Art Unit 1656

/Delia M. Ramirez/

Delia M. Ramirez, Ph.D.
Primary Examiner, Art Unit 1652